L2: Entry 9 of 12 File: USPT Mar 31, 1998

DOCUMENT-IDENTIFIER: US 5733523 A
TITLE: Targeted delivery of a therapeutic entity using complementary oligonucleotides

Priority Application Year (1):
1990

Brief Summary Text (5):
In so-called "anti-sense oligonucleotide" therapy, synthetic, modified DNA or RNA fragments, which may or may not be conjugated with enzymes or cytostatics, are directed towards complementary nucleic acid sequences (DNA or RNA) which are present in the "target" cells, for example of tumors or cells infected by a virus. Modification of the anti-sense oligonucleotide is necessary for the desired stability in circulation (inter alia, they must be able to withstand endogenous enzymes) and, in addition, the penetration in cells and tissues can be improved as a result of the modification. The anti-sense oligonucleotide is complementary to a nucleic acid sequence in the target cell and may inhibit DNA transcription, mRNA translation, or (viral) nucleic acid replication.

Detailed Description Text (12):
Another aspect of the invention provides a conjugate of a targeting moiety such as an antibody or a fragment or a derivative thereof, directed to an antigen associated with a target cell and a modified oligonucleotide which is complementary to a RAN. It is also possible to choose any other member of a specific binding pair which complementary member is associated with a specific group of target cells as a targeting moiety, such as ligands for receptors and the like. The conjugate can be administered to a subject; it will localize at the target site and after allowing sufficient time for said localization a RAN is administered, which will be bound by the complementary modified oligonucleotide in the conjugate. This will greatly enhance the possibilities of targeted therapy as used in for instance the combat of (auto) immune diseases, viral infections and tumors. Such a pretargeting program is shown in scheme 1. ##STR2##

Detailed Description Text (26):
The invention further comprises a kit of parts for the elimination of specific cell populations. Such kit of parts comprises one or more dosage units containing a composition comprising a modified oligonucleotide labelled with a therapeutically active radio-isotope (preferably the oligonucleotide of type I), and one or more dosage units containing a composition comprising a conjugate of an antibody or a fragment or a derivative thereof and a modified oligonucleotide (preferably of type II). The oligonucleotide moiety of the active ingredient of the first composition is complementary to the oligonucleotide moiety of the active ingredient (the nucleotide) of the second composition.

Detailed Description Text (27):
A method of treating viral infections, tumors and (auto)immunodiseases by sequentially administering the oligonucleotides of the invention to patients is also an objective of the invention. A conjugate comprising a modified oligonucleotide, preferably the conjugate of type II is then administered in a therapeutically effective dosage, followed by administering a therapeutically effective dosage of an oligonucleotide comprising a therapeutically active radio-isotope, preferably the oligonucleotide of type I (RAN), of which the oligonucleotide moiety is complementary to the oligonucleotide moiety of the conjugate. The time between the administration of both

components can vary from a few hours to 20 days. Preferably the second component is administered when the first component is bound by the target cell, which process can often be followed, for example when the conjugate is labelled with a diagnostic isotope (e.g. a gamma-emitter), by monitoring the patient. Sometimes it is necessary to repeat the first treatment with the conjugate to effect complete saturation. In individual cases the time schedule can be adapted in order to obtain a maximum effect.